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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,154	12/10/2001	Ryusuke Nakagiri	2139.27	2545

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FITZPATRICK CELLA HARPER & SCINTO
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NEW YORK, NY 10112

EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/010,154	NAKAGIRI ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 1-25-07 is acknowledged.

Claims included in the prosecution are 37 and 43-44.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 37 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thiele et al (5,939,535) in combination with Karmali (6,184,227) and Yamahara et al (Nature Medicines, 1995), JP 10046142 (both are of record), the last two references by themselves or together.

Thiele et al disclose that alcohol causes increase in the levels of lipid peroxidation, acetaldehyde and malondialdehye, which cause liver injury. According to Thiele et al, malondialdehye is formed by the peroxidation of polyunsaturated fatty acids and from the oxidative degradation of deoxyribose by a hydroxy free radical (col. 1, line 15 through col. 2, line 40). What is lacking in Thiele et al is the protection of the liver function from damage from excessive consumption of alcohol.

Karmali discloses that the administration of antioxidants inhibits the oxidation of ethanol and the toxic effects of acetaldehyde (col. 3, line 45 through col. 4, line 22). Karmali however, does not teach the administration of ethanolic extracts of Hydrangea.

Yamahara et al disclose that the methanol extract of Hydrangea Dulcis Folium exhibits strong radical inhibiting effect and inhibitory effect on oxidation of lipids (page 2, lines 7-9 and Experiment on pages 2-6 of the English translation).

JP discloses extracts of Saxifrage stolonifera exhibit marked and potent antioxidant effect compared to conventional antioxidants (English abstract).

In essence the references of Thiele et al and Karmali show the increases in lipid peroxidation and the production of reactive aldehydes caused by ethanol consumption and the inhibitory effect of antioxidants on the lipid peroxidation and the production of reactive aldehydes. It would have been obvious to one of ordinary skill in the art to use the extracts of Hydrangea Dulcis Folium or Saxifrage in the teachings of Thiele et al and Karmali to protect the liver function from alcohol since the references of Yamahara et al and JP teach the strong inhibitory action on the free radicals exhibited by these extracts.

Applicant's arguments have been fully considered, but are not persuasive. In response to the examiner's statement that Karmali discloses that the administration of antioxidants inhibits the oxidation of ethanol and the toxic effects of acetaldehyde, applicant argues that the examiner is incorrect and that rather in Karmali, the effective essential component to inhibit the oxidation of ethanol and the toxic effects of acetaldehyde to aminoimidazole caroxamide (AICA) and not antioxidants. The examiner agrees with applicant that one of the components in Karmali is AICA; however, Karmali is clearly suggestive of the function of the antioxidants in inhibiting the oxidation of ethanol and inhibiting the liver damage caused by ethanol. This is evident from several locations in Karmali. For example, on col. 7, lines 35-38, Karmali states, "In the present

invention, administration of salts of AICA results in inhibition of thromboxane A2, enhanced antioxidant defenses against lipid peroxides and free radicals". On col. 6, lines 1-35, Karmali teaches that ethanol oxidation results in the formation of acetaldehyde and acetaldehyde is the key factor in the hepatic injury caused by ethanol. On col. 5, lines 46-49, Karmali states, "IT may be that the ability of AICA salts alone or in combination with antioxidants, to detoxify harmful and noxious agents, to inhibit bioactivation of agents to harmful electrophiles or free radicals---". From these teachings it would have been obvious to one of ordinary skill in the art that antioxidants themselves have a preventive function in alcohol conversion to acetaldehyde and the toxic effects of acetaldehyde. Furthermore, the last teaching (that is, col. 5, lines 46-49) by Karmali implies that AICA has an antioxidant function since it inhibits lipid peroxides and free radicals. Applicant's arguments that Yamahara does not teach that the methanol extract of Hydrangea contains AICA. This argument is not persuasive since this reference is combined for its teachings of antioxidant function of the methanol extract of Hydrangea by its strong free radical inhibition and inhibition of the oxidation of lipids. Therefore, one of ordinary skill in the art would be motivated to use this antioxidant with the expectation of obtaining at least similar antioxidant function exhibited by other antioxidants. Applicant's arguments that those of ordinary skill in the art are also well aware that liver injuries such as hepatonecrosis cannot be protected only by inhibiting lipid peroxidation as evidenced by Suzuki reference. This argument is not persuasive since the claims are drawn to protecting liver function from damage and not to method of inhibiting hepatonecrosis. The rationale behind applicant's arguments

that JP discloses that extracts of Saxifrage stolonifera exhibit better antioxidant properties than conventional antioxidants and however, the pending claims do not recite Saxifrage Stolonifera are unclear since according to instant specification, 'the plant of the family of Saxifragaceae is a plant belonging to Hydrangea (see the amendment made to the specification, page 3 on 10-7-05). JP provides motivation for one of ordinary skill in the art to use extracts from a plant belonging to Genus Hydrangea, which possess compounds exhibiting stronger antioxidant properties than conventional antioxidants. The rejection is maintained.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK